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HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
ROARK, JESSICA H	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/870,932	Applicant(s) WU ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75-110* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75-110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 October 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7-9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. In the amendment filed 10/22/02 the numbering of claims is not in accordance with 37 CFR 1.126. Two claims each numbered 87 were filed, whereas no claim 86 was filed. Also, two claims each numbered 99 were filed, whereas no claim 98 was filed.

The first claim numbered 87 has been renumbered as claim 86, and the first claim numbered 99 has been renumbered as claim 98.

2. Applicant's amendment, filed 10/22/02 (Paper No. 12), is acknowledged.
Claims 1-73 have been canceled. Claim 74 has been canceled previously.
Claims 75-110 have been added and are pending.

3. Applicant's election of Group I in Paper No. 13 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 75-110 *are under consideration in the instant application.*

IDS

4. Applicant's IDSs, filed 4/25/01, 10/5/01 and 6/4/02 (Paper Nos. 7-9) are acknowledged. Parent application 08/893,911 is temporarily unavailable to the Examiner; thus references provided in the parent application have been considered only with respect to those references currently available to the Examiner. It should be possible to consider those references not considered (i.e., those references not initialed on the copy of the PTO-1449s provided) at a later date. Alternatively, Applicant is invited to re-supply these remainder of the references in order to complete the instant file.

A new 1449 is NOT required. A completely initialed copy will be returned to Applicant using the current 1449 of record.

Specification

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

Priority

7. USSN 08/739,507 appears to provide adequate written support for claims 75-80, 82, 86-92, 94, 98-104, 106 and 110; therefore these claims are considered to have an effective filing date of 10/28/96.

Claims 81, 83-85, 93, 95-97, 105 and 107-109 do not appear to have adequate written support in USSN 08/739,507 with respect to the limitations of "human", "second extracellular loop", and "hybridoma deposited under ATCC Accession No. HB-12366" (the 2D7 antibody-producing hybridoma). These limitations do appear to have adequate written support in USSN 08/893,911; therefore the effective filing date for these claims is considered to be 7/11/97.

8. Applicant should amend the first line of the specification to indicate the status of each parent application.

Claim Rejections - 35 USC § 112 first paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 83, 85, 95, 97, 107 and 109 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In claims 83, 85, 95, 97, 107 and 109, it is apparent that the antibody produced by the hybridoma deposited under ATCC Accession No. HB-12366 is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification.

It is noted that the specification on page 13 indicates that the 2D9-antibody-producing hybridoma cells were deposited with the ATCC as HB-12366 on 6/6/1997.

However, the specification does not indicated that the deposit was made to the conditions under the Budapest Treaty. In addition, Applicant is required to assure that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications (see 37 CFR 1.808 (a)(2) and MPEP 2410-2410.01).

It is acknowledged that Applicant has provided the necessary assurances in the 1.806 and 1.808 Declaration filed as Paper No. 13 *of parent application USSN 08/893,911, now allowed.* However, parent application USSN 08/893,911 has not yet issued. In addition, parent application USSN 08/893,911 is temporarily available to the Examiner such that the Examiner is unable to make of record in the instant case the Declaration filed in USSN 08/893,911.

Therefore, the enablement requirements of 35 U.S.C. 112, first paragraph at present are not fulfilled. However, it is noted that the enablement requirements with respect to the antibody produced by the hybridoma deposited under ATCC Accession No. HB-12366 will be considered fulfilled upon the issuing of parent application USSN 08/893,911 as a U.S. Patent; *and/or* upon receipt of a copy of the assurances filed in parent application USSN 08/893,911.

11. Claims 75-82, 84-94, 96-106 and 108-110 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies that inhibit binding of the chemokines MIP-1α, MIP-1β, RANTES to human CCR5; does not reasonably provide enablement for antibodies which inhibit binding of other "chemokines" to any "mammalian" CCR5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficient enabling description of the instantly claimed invention. A person of skill in the art is not enabled to make and use an antibody which inhibits binding of *any* "chemokine" to *any* "mammalian" CCR5 as encompassed by the full breadth of the claims as currently recited.

The specification appears to disclose only human CCR5, and that only the chemokines MIP-1α, MIP-1β, and RANTES bind human CCR5. There is insufficient guidance in the specification to direct a person of skill in the art in how to make and use an antibody which inhibits binding of *any* "chemokine", other than MIP-1α, MIP-1β, and RANTES, particularly when the chemokine may bind a CCR5 of *any* mammalian origin. Similarly, there is insufficient guidance in the specification to direct a person of skill in the art in how to make and use an antibody which inhibits binding of a chemokine to CCR5 from any mammal.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The term "chemokine" as recited encompasses *any* chemokine that binds CCR5. However, while MIP-1α, MIP-1β, RANTES are known to bind CCR5, the skilled artisan could not reasonably predict what other chemokines would also bind CCR5. For example, Zlotnik and Yoshie (Immunity 2000;12:121-127, IDS #AZ4) review that chemokine receptors such as CCR5 are known to interact with multiple chemokine ligands (see for example Table 1). Thus the skilled artisan would be required to conduct undue experimentation to identify all chemokines and test each for binding to CCR5 before these chemokines could be used to assay antibody inhibition of the chemokine binding as recited.

The specification also does not provide sufficient guidance as to how the skilled artisan may identify, without undue experimentation, any other mammalian ortholog of human CCR5 and make and use antibodies to these other "mammalian" CCR5 proteins. The state of the art recognized that identification of orthologous polypeptides required extensive experimentation in order to identify a candidate polypeptide from additional species (i.e., polypeptides with similar sequence) and then ascertain whether that polypeptide possessed functional similarities sufficient to justify it assignment as an ortholog of a polypeptide previously identified in another species. Thus the instant claims are essentially a wish to know the identity of any polypeptide which can be construed to be an "ortholog" of the instant human CCR5 protein and to make antibodies to these other "mammalian" proteins. It has been previously decided that claims recitations so broad do not provide sufficient guidance as to how to make and use the claimed invention. See Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Since it is unpredictable as to which other "chemokines" would bind CCR5 and could be inhibited by antibody binding, and as to the identity of other "mammalian" CCR5; the experimentation left to those skilled in the art to make and use the antibodies as currently broadly recited is unnecessarily, and improperly, extensive and undue.

12. Claims 75-82, 84-94, 96-106 and 108-110 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

There does not appear to be an adequate written description in the specification as-filed of the essential structural feature of a "chemokine" that provides the recited function of binding CCR5 and thus for antibodies which inhibit binding of any chemokine. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Thus although three species of chemokines that bind CCR5 are disclosed, there does not appear to be an adequate written description of the genus because no structural basis is identified for their binding function, and because the genus of chemokines was well known in the art to be large, particularly when the chemokine can bind to any mammalian CCR5.

Similarly, the specification discloses that a mammalian ortholog of a human CCR5 protein may be isolated from *any* mammalian species (page 19, lines 11-28). The genus of CCR5 proteins to which the instantly recited antibodies bind is therefore very large and a great deal of sequence variation is encompassed by the instant claims. In turn, the sequence variation among "mammalian" CCR5 proteins results in a highly diverse population of antibodies that bind "mammalian" CCR5. As noted supra the specification discloses only human CCR5. Thus the specification provides a single member of the instant genus of CCR5 proteins bound by the instantly recited antibodies. In University of California v. Eli Lilly and Co., 39 USPQ2d 1225 (Fed. Cir. 1995); the inventors claimed a genus of DNA species encoding insulin in different vertebrates or mammals, but had only described a single species of cDNA which encoded rat insulin. The Court held that only the nucleic acids species described in the specification (i.e. nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, id. at 1240. Therefore, the specification does not provide sufficient written support for the genus of polypeptides that includes any "mammalian" CCR5 protein. Consequently, adequate written support is lacking for the broader genus of antibodies which bind any "mammalian" CCR5.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See also University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

Claim Rejections – 35 U.S.C. §§ 102 and 103

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 75-82, 84-94 and 96-98 are rejected under 35 U.S.C. 102(e) as being anticipated by Li et al. (US Pat. No. 6,025,154, IDS AE, see entire document) *as evidenced by* Wu et al. (J. Exp. Med. 1997; 186(8):1373-1381, IDS #AS4).

Li et al. teach an antibody to human HDGNR10 (see entire document, especially column 18). HDGNR10 is the same protein as human CCR5 (see e.g., SEQ ID NO:2).

Li et al. teach that an antibody to HDGNR10 may be a monoclonal, chimeric, single chain, humanized or human antibody, or fragments thereof that include Fab fragments or single chain Fv fragments (e.g., column 18, especially lines 1-36). Li et al. also teach compositions and kits comprising said antibodies (e.g., see column 13 in view of column 12).

Li et al. also teach assays for screening for antagonists of both ligand binding and receptor function associated with that binding (see especially columns 11-12). Li et al. also clearly contemplate that an antibody to CCR5 was such an antagonist and could be produced and identified by the appropriate screen (see especially column 12 at lines 16-21 in view of columns 11-12 and 18). Thus while the disclosure of genus may not anticipate a species unless some direction is provided to that species; in the instant case the teachings of Li et al. do direct the ordinary artisan to screen for and select those anti-CCR5 antibodies having the instantly recited functional properties of inhibiting binding of a chemokine (i.e., a CCR5 ligand) and inhibiting (i.e., antagonizing) one or more functions associated with binding.

Wu et al. evidence that those antibodies which block binding of the chemokines MIP-1α, MIP-1β and RANTES to CCR5 bind the second extracellular loop of CCR5 (see entire document, especially bridging paragraph of pages 1375 and 1376).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations of inhibiting binding of the chemokines MIP-1α, MIP-1β and RANTES; of binding to the second extracellular loop; or of competing with the antibody of HB-12366; would all be inherent properties of the antibodies taught by Li et al.

The reference teachings thus anticipate the instant claimed invention.

15. Claims 75-82, 84-94 and 96-98 are rejected under 35 U.S.C. 102(e) as being anticipated by Hoxie (US Pat No. 5,994,515, IDS AB, see entire document) *as evidenced by* Olson et al. (J. Virol. 1999; 73:4145-4155, IDS #AW5) and Wu et al. (J. Exp. Med. 1997; 186(8):1373-1381, IDS #AS4).

Hoxie teaches and claims an antibody to the HIV coreceptor human CCR5 (see entire document, especially Claims). Hoxie teaches that an antibody may be a monoclonal, chimeric, human, or humanized antibody, or fragments thereof, including single chain or Fab fragments (see especially columns 9-10 and 12). Hoxie teaches formulation of these antibodies in compositions (e.g., columns 11-12).

Hoxie teaches methods of making antibodies in various forms which bind HIV coreceptors and selecting for those antibodies which inhibit HIV infection (see column 8, especially lines 18-20, and columns 17-19). While Hoxie only produces an antibody to CXCR4 that blocks HIV entry, the teachings of Hoxie clearly indicate that the same methodology was applicable to the other known HIV co-receptor, CCR5 (see e.g., the "Background of the Invention" at columns 1-2, "Summary of the Invention" at columns 2-3 and column 19). Hoxie acknowledges that CCR5 was known in the art (see especially column 1 at lines 37-45 and column 19), as was the binding of the chemokines MIP-1α, MIP-1β and RANTES to CCR5 (see especially column 2 at lines 25-29). Thus the teachings of Hoxie were sufficient to permit one of ordinary skill in the art to reduce to practice monoclonal antibodies to CCR5.

Wu et al. evidence that those antibodies which block binding of the chemokines MIP-1α, MIP-1β and RANTES to CCR5 bind the second extracellular loop of CCR5 (see entire document, especially bridging paragraph of pages 1375 and 1376).

The Examiner acknowledges that HIV co-receptor functions and functions associated with chemokine binding to CCR5 can be dissociated, as also taught by Wu et al. (see entire document). However, Olson et al. show that the antibodies *most effective* at inhibiting HIV membrane fusion and viral entry (assays of HIV infection) *are the antibodies that also inhibit calcium flux* (i.e., a function associated with binding of a chemokine to CCR5) in response to the chemokine RANTES binding to CCR5 (see especially Table 1 and the comments with respect to PA14 and 2D7 on pages 4147-4150). Thus a screen such as taught in Hoxie that assayed for inhibition of HIV infection (i.e., cell fusion and viral entry) would *necessarily* include antibodies that inhibited chemokine binding and one or more functions associated with chemokine binding to CCR5. Not only were such monoclonal antibodies produced upon immunization with CCR5, but based on the teachings of Hoxie to screen for inhibition of HIV infection, the ordinary artisan would clearly have selected for those monoclonal antibodies which also inhibited chemokine binding to CCR5 because those were the antibodies most effective at inhibiting HIV infection.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations of inhibiting binding of the chemokines MIP-1α, MIP-1β and RANTES; of binding to the second extracellular loop; or of competing with the antibody produced by the hybridoma deposited under ATCC accession No. HB-12366; would all be inherent properties of the monoclonal antibodies taught by Hoxie.

The reference teachings thus anticipate the instant claimed invention.

16. Claims 75-82, 84-94, 96-106 and 108-110 are rejected under 35 U.S.C. 102(e) as being anticipated by Littman et al. (US Pat. No. 5,939,320, IDS # AA, see entire document) *as evidenced by* Olson et al. (J. Virol. 1999; 73:4145-4155, IDS #AW5) and Wu et al. (J. Exp. Med. 1997; 186(8):1373-1381, IDS #AS4).

Littman et al. teach an antibody to human CC-CKR-5 (see entire document, especially columns 5 and 20-22). CC-CKR-5 is the same protein as human CCR5. Littman et al. teach that CC-CKR-5 is bound by the chemokines MIP-1α, MIP-1β and RANTES (e.g., column 2, especially lines 12-25).

Littman et al. teach that an antibody can be a monoclonal, chimeric, human or humanized antibody (see e.g., columns 20-21). Littman et al. also teach fragments of these antibodies including single chain, Fab, F(ab')2 and Fab' fragments (e.g., column 21, especially lines 25-44). Kits comprising these anti-CCR5 antibodies and ancillary reagents for detecting the antibody bound to CCR5 are also taught (see especially columns 6 and 22-23).

Littman et al. describe assays for inhibition of various steps associated with HIV infection, as well as for inhibition of HIV infection (e.g., see columns 20, 21, 23-24 and especially column 31).
Applicant's arguments with respect to the inherency of the instantly recited functions in antibodies selected for inhibition of HIV infection and that there is no requirement that such antibodies actually be produced have been discussed supra with respect to Hoxie. To summarize those arguments, while the data do show that HIV co-factor functions and functions associated with chemokine binding are dissociable, that two functions may be dissociated does not indicate that an antibody that inhibits HIV would not inherently block binding of chemokines to CCR5. As discussed in detail supra, antibodies which inhibit chemokine binding and functions associated with chemokine binding have been found to be those that are most efficient at inhibiting CCR5 co-receptor activity. Thus a screen such as taught in Littman et al. that assayed for inhibition of HIV infection would necessarily include antibodies that inhibited chemokine binding and one or more functions associated with chemokine binding to CCR5. Not only did such antibodies exist, but based on the teachings of Littman et al. to screen for inhibition of co-receptor function the ordinary artisan would clearly have selected for those antibodies because they were most effective at inhibiting HIV infection.

Wu et al. evidence that those antibodies which block binding of the chemokines MIP-1α, MIP-1β and RANTES to CCR5 bind the second extracellular loop of CCR5 (see entire document, especially bridging paragraph of pages 1375 and 1376).

The Examiner acknowledges that HIV co-receptor functions and functions associated with chemokine binding to CCR5 can be dissociated, as also taught by Wu et al. (see entire document). However, Olson et al. show that the antibodies *most effective* at inhibiting HIV membrane fusion and viral entry (assays of HIV infection) *are the antibodies that also inhibit calcium flux* (i.e., a function associated with binding of a chemokine to CCR5) in response to the chemokine RANTES binding to CCR5 (see especially Table 1 and the comments with respect to PA14 and 2D7 on pages 4147-4150). Thus a screen such as taught in Hoxie that assayed for inhibition of HIV infection (i.e., cell fusion and viral entry) would *necessarily* include antibodies that inhibited chemokine binding and one or more functions associated with chemokine binding to CCR5. Not only were such monoclonal antibodies produced upon immunization with CCR5, but based on the teachings of Littman et al. to screen for inhibition of various steps of HIV infection, the ordinary artisan would clearly have selected for those monoclonal antibodies which also inhibited chemokine binding to CCR5 because those were the antibodies most effective at inhibiting HIV infection.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations of inhibiting binding of the chemokines MIP-1α, MIP-1β and RANTES; of binding to the second extracellular loop; or of competing with the antibody produced by the hybridoma deposited under ATCC accession No. HB-12366; would all be inherent properties of the antibodies taught by Littman et al.

The reference teachings thus anticipate the instant claimed invention.

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 75-79, 84-85, 87-91, 96-97, 99-103 and 108-109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chuntharapai et al. (US Pat. No. 5,543,503, IDS AD) in view of *either* Raport et al. (J. Biol. Chem. 271:17161-17166 1996, IDS # AW), Samson et al. (Biochem. 35:3362-3367 1996, IDS #AV), *or* Combadiere et al. (J. Leukoc. Biol. 60:147-152 1996, IDS #AT3), *as evidenced by* Wu et al. (J. Exp. Med. 1997; 186(8):1373-1381, IDS #AS4).

The claims are drawn to monoclonal antibodies that bind to mammalian or human CCR5 and that inhibit binding of the chemokine ligands MIP-1α, MIP-1β, and RANTES and functions associated with chemokine binding. The claims are also drawn to antibodies that bind the second extracellular loop of CCR5 and to antibodies that compete with the antibody produced by the hybridoma deposited under ATCC Accession No. HB-12366. The claims are also drawn to compositions and kits comprising said antibodies.

Chuntharapai et al. teach the production of monoclonal antibodies that can inhibit binding of the chemokine IL-8 to its receptor (see entire document, e.g., "Summary of the Invention"). Chuntharapai et al. also teach that this method can be applied to all members of the PF4A superfamily, which includes the CXC chemokine receptors such as the IL-8 receptor, and also includes the receptors of CC chemokines such as RANTES (see especially columns 1 and 2). Chuntharapai et al. provide methods of antibody production and screening for monoclonal antibodies that block interaction of the chemokine with its receptor by providing the example of blocking antibodies to the IL-8R (see entire document, especially Example 3 of columns 35-39; as well as columns 29-30). Thus Chuntharapai et al. provide an assay for the production of monoclonal antibodies that inhibit the interaction of the chemokine with its receptor.

Chuntharapai et al. teach that antagonist antibodies can also be screened for their ability to block activation of IL-8R-expressing cells (e.g. column 30, especially lines 20-31 and also see "Summary of the Invention, especially lines 33-41). One of ordinary skill in the art would have certainly understood that these statements by Chuntharapai et al. indicated that not only was inhibition of chemokine binding by the antibody desirable (and a property of the antibody which for which a screen existed); but also inhibition of the functions normally associated with binding of the chemokine to its receptor. In addition, Chuntharapai et al. also teach that it is such antagonist antibodies that are therapeutic candidates (see e.g. column 30 at lines 21-31). Finally, it is noted that many assays for inhibition of a function associated with the binding of the chemokine IL-8 were well known in the art at the time of Chuntharapai's teachings, as reviewed in the "Background of the Invention" at columns 1-2.

Chuntharapai et al. teach formulation of antibodies as compositions for use in a variety of methods, including detection of the receptor on cells using an ancillary reagent (i.e., a label) for detecting the formation of the antibody: receptor complex (e.g., column 30 at line 66 to column 33 at line 38).

Each of Raport et al., Samson et al. and Combadiere et al. teach human CCR5, although the protein is also referred to as CC CKR5 (see entire document of each, e.g., the Abstracts). Each of Raport et al., Samson et al. and Combadiere et al. further teach that the chemokines ligands of human CCR5 are MIP-1α, MIP-1β, and RANTES (see entire document, e.g., Abstracts). The Materials and Methods sections of each of Raport et al., Samson et al. and Combadiere et al. also provide binding assays and assays for receptor activation. Thus each reference teaches the human chemokine receptor CCR5, the chemokine ligands which bind human CCR5, and assays which allow inhibitors of the binding of the ligands to the receptor to be identified. Each reference also reviews in their Introduction that chemokines are important mediators of inflammation via recruitment of leukocytes.

Given the teachings of Chuntharapai et al. that antibodies can inhibit binding of chemokines to the chemokine receptor; in view of the teachings of Raport et al., Samson et al. and Combadiere et al. that CCR5 is the chemokine receptor for MIP-1α, MIP-1β, and RANTES, and that these chemokines are important mediators of inflammation via their recruitment of leukocytes expressing CCR5; the ordinary artisan at the time the invention was made would have been motivated to produce monoclonal antibodies to CCR5 that blocked binding of the MIP-1α, MIP-1β, and RANTES chemokine ligands of CCR5, and therefore blocked their recruitment function. Chuntharapai et al. provide a methodology for producing such monoclonal antibodies when the receptor sequence is known. Raport et al., Samson et al. and Combadiere et al. each provide the human CCR5 sequence, and further identify the MIP-1α, MIP-1β, and RANTES chemokine ligands of human CCR5 and assays for blocking one or more functions associated with binding of these chemokines to CCR5.

Thus the ordinary artisan at the time the invention was made would have had a reasonable expectation of success not only for producing monoclonal antibodies to human CCR5 in general, but of producing antibodies to human CCR5 that blocked binding of the chemokine ligands MIP-1α, MIP-1β, and RANTES and that inhibited their function (i.e., that were antagonists).

Wu et al. evidence that those antibodies which block binding of the chemokines MIP-1α, MIP-1β and RANTES to CCR5 bind the second extracellular loop of CCR5 (see entire document, especially bridging paragraph of pages 1375 and 1376). In addition, antibodies which block binding of chemokine ligands to CCR5 would compete with the antibody produced by the hybridoma deposited under ATCC Accession No. HB-12366, because (as also shown by Wu et al. ibid), the 2D7 antibody produced the hybridoma of ATCC Accession No. HB-12366 binds the second extracellular loop of CCR5.

Given the applications taught by Chuntharapai et al. in general in view of the known functions of CCR5 as taught by each of Raport et al., Samson et al. and Combadiere et al., the ordinary artisan would have been motivated to formulate the human CCR5 specific antibodies and fragments thereof in compositions for use in various methods as taught by each of the references. In addition, given the teaching of Chuntharapai et al. that the antibody could be used to detect the receptor on cells by using the antibody to the receptor and a reagent to detect the antibody; the ordinary artisan would have been motivated to formulate the instant antibodies and ancillary reagent for detecting the formation of the antibody: receptor complex as kits for convenience and economy in methods. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. Claims 80-82, 86, 92-94, 98, 104-106 and 110 are rejected under 35 U.S.C. 103(a) as being unpatentable over

Chuntharapai et al. (US Pat. No. 5,543,503, IDS AD) in view of *either* Raport et al. (J. Biol. Chem. 271:17161-17166 1996, IDS # AW), Samson et al. (Biochem. 35:3362-3367 1996, IDS #AV), *or* Combadiere et al. (J. Leukoc. Biol. 60:147-152 1996, IDS #AT3), *as evidenced by* Wu et al. (J. Exp. Med. 1997; 186(8):1373-1381, IDS #AS4),

as applied to claims 75-79, 84-85, 87-91, 96-97, 99-103 and 108-109 above;
and further in view of Ramakrishnan et al. (US Pat. No. 5,817,310, see entire document).

The claims are drawn to a chimeric, human or humanized antibody, or fragments (e.g., Fab/F(ab')$_2$) thereof, that binds to mammalian or human CCR5 and inhibits binding of the chemokine ligands MIP-1α, MIP-1β, and RANTES and functions associated with chemokine binding. The claims are also drawn to compositions and kits comprising said antibodies.

Chuntharapai et al. in view of any of Raport et al., Samson et al. and Combadiere et al. et al. have been discussed supra.

Chuntharapai et al. in view of any of Raport et al., Samson et al. and Combadiere et al. et al. differ by not teaching chimeric, human, humanized or Fab/F(ab')$_2$ fragments of the antibody.

However, one of ordinary skill in the art at the time the invention was made recognized that there were many ways to produce an antibody, and that the various forms of antibody were art-recognized variants of one another. For example, Ramakrishnan et al. teach that the ordinary artisan at the time the invention was made recognized that antibodies could be formulated in any of a variety of interchangeable forms for use as compositions comprising a pharmaceutically acceptable carrier in a variety of art recognized assays to detect a protein of interest (see entire document, especially columns 8-17). Ramakrishnan et al. teach that antibodies could be single chain antibodies, Fab fragments, or F(ab')$_2$ fragments (see e.g. column 9 at lines 9-27 and column 14 at lines 62-65).

One of ordinary skill in the art at the time the invention was made was also well aware that for many applications, particularly therapeutic applications, antibodies that were chimeric, human or humanized, or fragments thereof were highly desirable and particularly preferred forms of antibodies. For example, Ramakrishnan et al. teach chimeric, human and humanized antibodies at columns 8-17, especially columns 13-14). Ramakrishnan et al. teach that it is desirable to prepare antibodies to the antigen of interest that are substantially human for administration of the antibody to a human (see e.g., columns 13-14, especially column 13 at lines 50-65). Compositions comprising antibodies in a pharmaceutically acceptable carrier, and various art recognized applications of antibodies for detection are taught in columns 15-17.

It would have been obvious to the ordinary artisan at the time the invention was made to prepare antibodies to CCR5 in any of the instantly recited forms for use in art-recognized applications such as those taught by Chuntharapai et al. or Chuntharapai et al. in view of any of Raport et al., Samson et al. and Combadiere et al. et al. Given the teachings of Raport et al., Samson et al. and Combadiere et al. that chemokines are important mediators of inflammation via recruitment of leukocytes, and the teachings of Chuntharapai et al. that antibodies could be used as antagonists; it would have been obvious to the ordinary artisan at the time the invention was made to prepare antibodies to human CCR5 that were chimeric, human or humanized in order to provide reagents that could be administered to a human. The ordinary artisan would have been motivated to make chimeric, human or humanized forms of antibodies to CCR5 because the ordinary artisan recognized the advantage of antibodies in these particular forms for applications involving administering the antibody to a human. Given the well-developed methods for producing these forms of antibodies, as taught by Ramakrishnan et al.; the ordinary artisan at the time the invention was made would have had a reasonable expectation of making chimeric, human or humanized antibodies to human CCR5. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 75-110 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over allowed claims 1-36 of copending Application No. USSN 08/893,911, now allowed. Although the conflicting claims are not identical, they are not patentably distinct from each other because the species of anti-CCR5 antibodies claimed in USSN 08/893,911 either anticipate or render obvious the generic claims set forth in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
January 9, 2003

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
1/9/03